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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	22

DATE MAILED: 09/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/689,992	MELLO ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,17-22 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,17-22 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .

4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to an amendment filed on May 15, 2003. Claims 1-14 and 17-34 were previously pending, with claims 1-13 and 23-34 withdrawn from consideration. In the current amendment Applicants provided an instruction to cancel claims 1-13 and 17-34 on page 2, but in the remarks on page 3 Applicants state that claims 1-13 and 23-34 are cancelled, and pages 15-16 list pending claims, 14 and 17-22, with a newly added claim 35. Therefore it is assumed that Applicants' intention was to cancel claims 1-13 and 23-34. Claims 14, 17-22 and 35 are pending and will be examined.

2. Objection to drawings regarding replacement of SEQ ID NO: 3 with SEQ ID NO: 13 in Fig. 4B is withdrawn.

3. Objection to specification regarding changes in the sequence listing is maintained. Applicants submitted new sequence listing on June 2, 2003, which "... corrects inadvertent errors that were made in the originally submitted sequence listing...". Applicants do not explain what the errors were and why the sequence listing had to be corrected. The new sequence listing contains 14 sequences instead of the original 15. Applicants did not explain why one of the sequences was removed, and what other changes were made to the sequence listing.

4. Rejection of claims 14 and 17-22 under 35 U.S.C, first paragraph, enablement, is withdrawn.

5. Applicants' arguments are moot in view of new grounds for rejection, which are presented below.

Specification

6. The amendment filed on August 12, 2002 and a sequence listing submitted on June 2, 2003 are objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

The added material which is not supported by the original disclosure is as follows: new sequence listing was submitted, which "… corrects inadvertent errors that were made in the originally submitted sequence listing…". Applicants do not explain what the errors were and why the sequence listing had to be corrected. The new CRF and sequence listing submitted on June 2, 2003, contain 14 sequences instead of the original 15. Applicants did not explain why one of the sequences was removed, and what other changes were made to the sequence listing.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 14, 20-22 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants define an RNAi agent as a double-stranded RNA (dsRNA) molecule wich has been treated with those components of the RNAi pathway that are recognized to confer RNAi activity on the dsRNA. In the case of *C. elegans*, these components were determined to be RDE-1 and RDE-4 proteins (specification, page 6, lines 14-17). An RNAi pathway component is defined as a protein or nucleic acid that is involved in promoting dsRNA-mediated interference (page 5, lines 9-12). The term "RNAi pathway polypeptide" is defined by Applicants as "naturally occurring RNAi pathway polypeptide such as RDE-1 protein or RDE-4 protein, as well as

recombinantly produced polypeptides that correspond to a full-length, naturally occurring RDE-1 protein, RDE-4 protein, or to particular domains or portions of a naturally occurring RNAi pathway protein" (page 3, lines 23-28). In *C. elegans*, the components of the RNAi pathway were determined to be genes rde-1, rde-2, rde-3, rde-4, rde-5, mut-2 and mut-7 (page 2, lines 11-31).

Applicants cloned the rde-1 and rde-4 genes, but did not express the encoded proteins (Examples 6 and 11). Example 12 (page 48) outlines theoretical steps to be taken to determine which parts of RDE-1 or RDE-4 proteins are necessary to create an RNAi agent, but the experiments were not performed by Applicants.

Gene silencing using dsRNA has been observed in several organisms, such as fruit fly *Drosophila melanogaster* (Misquita et al., PNAS USA, vol. 96, pp. 1451-6, February 1999; Kennerdell et al., Cell, vol. 95, pp. 1017-26, December 1998; both cited in the IDS), metazoans (Sanchez Alvarado et al., PNAS USA, vol. 96, pp. 5049-54, April 1999; cited in the IDS), Trypanosoma brucei (Ngo et al., PNAS USA, vol. 95, pp. 14687-92, December 1998; cited in the IDS) and plants (Waterhouse et al., PNAS USA, vol. 95, pp. 13959-64, November 1998; cited in the IDS). However, no specific genes or gene products were identified which could be classified as "components of the RNAi pathway" in these organisms.

Therefore, taking into account the facts that:

a) the term "RNAi pathway component" is defined by only by its function of "conferring RNAi activity", which can also mean any nucleic acid or protein which influences already known pathway components,

b) only two proteins, RDE-1 and RDE-4 and seven genes (rde-1, rde-2, rde-3, rde-4, rde-5, mut-2 and mut-7) and only in *C. elegans* were determined to belong to the RNAi pathway,

c) it is not known which fragments or domains of RDE-1 or RDE-4 are necessary for the activity as an RNAi polypeptide,

d) no other RNAi pathway components were determined in any other organisms, Applicants have described only nine species of a genus of potentially millions of different nucleic acids, polypeptides and polypeptide variants, fragments and domains from all possible organisms.

9. Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 17 is drawn to the method of claim 14 wherein the RNAi pathway component is an RDE-1 polypeptide, claim 18 is drawn to the method of claim 14 wherein the RNAi pathway component is an RDE-4 polypeptide, and claim 19 is drawn to the method of claim 14 wherein the RNAi pathway components are an RDE-1 polypeptide and an RDE-4 polypeptide.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of polypeptides which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the

particularly named SEQ ID Nos (SEQ ID NO: 3, 5, 13 and 14). Thus, applicant has express possession of only four particular polypeptides, in a genus which comprises millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. .Polypeptides RDE-1 and RDE-4 have not been identified either structurally or functionally. No structural limitations or requirements which provide guidance on the identification of sequences which meet the limitations is provided. No functional limitations, other than being a component of an unspecified "RNAi pathway" have been provided. Further, these claims encompass alternately spliced versions of the proteins, allelic variants including insertions and mutations, inactive precursor proteins which have a removable amino terminal end, and only four specific amino acid sequences have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the RDE-1 and RDE-4 polypeptides lack any specific structure, is precisely the situation of naming a type of material which is generally known

to likely exist, but, except for the four specific polypeptides, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a major part of exon 13", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as component of the RNAi pathway, without any definition of the particular deletions claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any polypeptides other than those expressly disclosed which comprise SEQ ID NOs 3, 5, 13 and 14. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

10. Claims 14, 17-22 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting activity of a gene by dsRNA *in vitro*, does not reasonably provide enablement for inhibiting activity of a gene by dsRNA *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

MPEP 2164.01(a) Undue Experimentation Factors

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue." These factors include, but are not limited to:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention and breadth of claims

Claim 22 is broadly drawn to a method of inhibiting the activity of a gene, the method comprising introducing an RNAi agent into a cell, wherein the RNAi agent is prepared by incubating a double-stranded RNA (dsRNA) component in the presence of an RNAi pathway component, and wherein the dsRNA component is targeted to the gene, where the cell is in an animal. This claim is drawn to gene targeting by RNA interference in all animals, including mammals. However, as will be further discussed, there is no support in the specification and prior art for the *in vivo* method as applied to all animals. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Several references published before the priority date of the current application reported gene silencing using dsRNA in several organisms, such as fruit fly *Drosophila melanogaster* (Misquita et al., PNAS USA, vol. 96, pp. 1451-6, February 1999; Kennerdell et al., Cell, vol. 95, pp. 1017-26, December 1998; both cited in the IDS), metazoans (Sanchez Alvarado et al., PNAS USA, vol. 96, pp. 5049-54, April 1999; cited in the IDS), Trypanosoma brucei (Ngo et al., PNAS USA, vol. 95,

pp. 14687-92, December 1998; cited in the IDS) and plants (Waterhouse et al., PNAS USA, vol. 95, pp. 13959-64, November 1998; cited in the IDS), however, in mammalian cells there is an additional complication when one attempts gene silencing, as described by Montgomery et al. (Trends in Genetics, Vol. 14, pp. 255-8, July 1998; cited in the IDS). These cells exhibit a global antiviral response to dsRNA, in which the PKR protein kinase recognizes dsRNA and causes a non-specific response which results in general transcriptional arrest. "Any gene-specific interference by dsRNA in PKR-proficient mammalian cells would be dependent on a transient lapse in the PKR response, or on a controlled level of dsRNA that was incapable of activating PKR." (page 258, fourth paragraph).

Despite the progress in elucidation of the mechanisms of gene silencing, the results remain unpredictable, as indicated by recent references. In a review of double-stranded RNA interference, Heaphy et al. (Recent Res. Devel. Virol., vol. 3, pp. 91-104, 2001), teach that attempts to demonstrate RNAi in mammalian cells were unsuccessful (page 100, the last paragraph; page 101, first paragraph). In terms of future prospects for RNAi, Heaphy et al. state "Many components of mechanisms of RNAi will be described in the next few years. Points of contact with other RNA processing pathways in the cell will be identified." (page 101, the last paragraph) and "looking for evidence of RNAi in cell lines deficient in IFN response pathways seems worthwhile to us e.g. Vero cells or mouse cell lines lacking the PKR, RnaseL and Mx proteins. The rationale being that if the IFN effect generally masks RNAi then it will be more easily observed under these conditions." (page 102, the last paragraph). Therefore, two years after the priority date of the current application the RNAi needed to be extensively studied in mammalian cells.

Paddison et al. (Cancer Cell, vol. 2, pp. 17-23, July 2002), teach differences between responses to dsRNA in C. elegans and mammalian cells. In C. elegans, due to amplification of

RNAi signal mediated by RNA-dependent RNA polymerase (RdRP), RNAi signal amplification contributes to heritable, systemic gene silencing, whereas in mammalian cells the transfection of transient dsRNA triggers a transient effect, lasting 2-7 days. The factors involved in longevity of gene silencing involve abundance of mRNA and encoded protein, stability of the protein, transcriptional feedback loops, the half-life of the silencing complex and cell division (page 18, 8th paragraph). Even though gene silencing in mouse embryos and embryonal cell lines was observed, in somatic cells use of ~ 500 bp long dsRNA results in triggering apoptotic response mediated by PKR and RnaseL pathways. Even in cells in which PKR activity is removed, long dsRNA triggers a residual nonspecific repression of gene expression (page 18, fourth paragraph).

Finally, Paddison et al. point out that "RNAi holds promise for in vivo genetic application in mammals. Perhaps the most immediate question is whether expressed RNAi triggers can be combined with transgenic approaches for stably knocking down gene expression in rodents. … Studies of ex vivo modified cells can also benefit from RNAi, where primary or transformed cells are stably engineered with shRNAs and then implanted into mice.", and "RNAi shows tremendous promise as a new technology for manipulating gene expression for both experimental and therapeutic purposes. However, we are still in the very early stages of understanding both the mechanistic basis and biological roles of these gene-silencing pathways. Thus, we will undoubtedly see both spectacular successes and notable failures of RNAi before we fully understand the power and limitation of this new tool." (page 21, the last paragraph).

Caplan (Trends in Biotech., vol. 20, pp. 49-51, February 2002), points to the fact that gene silencing in somatic mammalian cells is hampered by the presence of pathways which trigger non-specific responses to dsRNA, such as the PKR interferon pathway, which mediates apoptosis, and the RnaseL pathway (page 50, second paragraph). Caplan states "It is probably too early to predict

how widely RNAi will be used in vertebrate cells because it is unclear whether all mammalian cell types can support RNAi and work is still required to determine the key parameters that will generate consistent RNAi against any given target." (page 50, fifth paragraph).

Finally, in the most recent of cited references, Scherr et al. (Current Med. Chem., vol. 10, pp. 245-256, February 2003) point to several factors which make gene silencing by dsRNA unpredictable: 1) mechanisms of RNAi in diverse organisms are not yet completely understood (page 246, last paragraph), 2) silencing efficiency depends on positional effects (page 249, second, third and sixth paragraph), 3) there are problems with delivery of dsRNA to cells due to liposome toxicity (page 249, last paragraph) or cell damage in electroporation (page 251, first paragraph), 4) the protein level of the gene targeted by RNAi depends on the rate of gene translation, therefore it is likely that RNAi will not entirely prevent protein synthesis from the targeted gene (page 252, third paragraph). Scherr et al. Conclude with the following statement « However, no effective methods to efficiently deliver siRNA to animals that could be adapted to human patients have yet been reported. … Whereas hydrodynamic transfection methods effective in mice cannot be translated into humans, injection of siRNA preparations into the portal vein might represent a modality to deliver siRNA to treat liver diseases such as hepatitis-C infection in the future. However, even if effective and pharmacological preparations to successfully deliver siRNAs into human patients are developed, the fact that RNAi usually inhibits but does not completely eliminate eliminate aberrant gene expression harbors the risk for the development of escape mutants." (page 253, last paragraph; page 254, first paragraph).

In summary, almost four years after the priority date of the current application, the mechanism of gene silencing by RNAi is still not fully understood and therefore unpredictable, and basic conditions for effective and stable gene silencing effects by RNAi still need to be determined.

The amount of direction provided by the inventor and working examples

The specification provides no evidence that the disclosed effects of gene inhibition by dsRNA in *C. elegans* can be translated to all other animals. Applicants provided evidence that pos-1, unc-22, sqt-3 and par-2 genes can be inactivated in *C. elegans* using dsRNA (Examples 3 and 4). In particular, the worms were provided with dsRNA in their feed (bacteria transfected with a plasmid harbouring the pos-1 gene, for example), which is certainly not a mechanism which could be used for all animals. No evidence or reasoning was provided that would enable a conclusion that all of the genes in all animals could be inhibited by such mechanism, or, for that matter, that all of the genes in C.elegans could be predictably silenced by RNAi. Therefore, the guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to in vivo methods in all animals. In particular, a skilled artisan wanting to use the method of the invention in vivo would need to determine at least the following: 1) the mechanism of RNAi gene silencing in a given organism, including all of the nucleic acids and proteins necessary for effective and stable gene silencing, 2) positioning of the dsRNA sequence with respect to the sequence being targeted to obtain effective gene silencing, 3) effects of the level of gene expression, protein stability, half0life of silencing complex, etc., on the longevity of the silencing effect, 4) the length of dsRNA to be administered to cells (in case of mammals) so that it does not trigger the PKR or RnaseL non-

specific responses, 5) efficient methods of delivery of the dsRNA to animal cells and ways to monitor the effectiveness of gene silencing.

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the effects of introduction of dsRNA into cells in vivo depend upon numerous known and unknown parameters such as the mechanism of gene silencing by dsRNA, effects of the level of gene expression and protein stability on the effectiveness and stabilityof gene silencing, presence of non-specific responses in mammalian cells, inefficient delivery of dsRNA to cells by currently used methods, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the dsRNA for in vivo gene silencing as broadly claimed (i.e encompassing a method in any animal cell under any conditions). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Interpretation

11. Claim 14 is interpreted as a method of inhibiting the activity of a gene, the method comprising introducing an RNAi agent into a cell, wherein the RNAi agent is dsRNA targeted to the gene. The limitation of preparing the RNAi agent by incubating a dsRNA in the presence of RNAi

pathway component is interpreted as incubation of dsRNA with the RNAi pathway components present in the cell into which the dsRNA is introduced.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 14, 21, 22 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Fire et al. (Nature, vol. 391, pp. 806-811, February 1998; cited in a previous office action).

Regarding claims 14 and 35, Fire et al. teach inhibiting activity of several *C. elegans* genes (*unc-22, fem-1, unc-54, hlh-1, myo-3-driven GFP transgene*) by introducing an RNAi agent (dsRNA) into C. elegans (Abstract, Table 1). Since all of these genes were inhibited by dsRNA introduced, the RNAi pathway components were present in these C. elegans cells.

Regarding claim 21, Fire et al. teach injection of dsRNA into *C. elegans* (page 810, paragraphs 6 and 7).

Regarding claim 22, Fire et al. teach introduction of dsRNA into *C. elegans* animals (page 810, paragraphs 6 and 7).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (Nature, vol. 391, pp. 806-811, February 1998; cited in a previous office action) and Wheeler et al. (U.S. Patent No. 5,976,567).

A) Claim 20 is drawn to the method of claim 14 wherein the RNAi agent is introduced into the cell in a liposome.

B) Fire et al. do not teach introduction of RNAi agent into a cell in a liposome.

C) Wheeler et al. teach liposomes for delivery of nucleic acids in vitro and in vivo (Abstract). In particular, Wheeler et al. teach liposomes for delivery of nucleic acids, including RNA, into cells (col. 11, lines 47-67; col. 12, lines 1-55).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used liposomes of Wheeler et al. to deliver the RNAi agent of Fire et al. into cells. The motivation to do so, provided by Wheeler et al., would have been that cationic lipid complexes were the most effective means of introducing non-viral nucleic acids into cells (col. 1, lines 54-56).

16. No claims are allowed. No references were found teaching or suggesting claims 17-19, but they are rejected for reasons given above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS

September 2, 2003 TS

JEFFREY FREDMAN
PRIMARY EXAMINER

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600